APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

1856 '99 MAR 25 P1:30

March 22, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr. Room. I-23
Rockville, MD 20857

RE: Comments Addressed to Docket Number 98D-1168
FDA Draft Guideline – ANDAs: Impurities in Drug Products

To Whom It May Concern:

Apotex Corp. has reviewed the above-listed draft guidance and proposes the following list of comments for your consideration.

For ease of reference, we have included the page and line numbers to which our questions/comments pertain.

I. INTRODUCTION

Line 5 -6: This section states the guideline covers, "degradation products of the active ingredient or reaction products of the active ingredients with excipient(s) and /or immediate container/closure systems. However, it does not mention whether secondary or tertiary degradants are covered. Additional clarification would be helpful.

IIII. IDENTIFYING AND REPORTING IMPURITIES

Line 72-75: This section discusses identifying impurities attributed to excipients. We suggest there be an addition to the end of the sentence that a comparison should be provided for the drug product and the placebo product **stored under identical conditions**. This will allow for degradation products of excipients to be differentiated from degradation products of the drug substance.

Line 87-99: This section discusses the comparison of degradation between the RLD and the generic. It requires use of reference standards if available. If not, then adequate structural characterization should be done to ID the degradation products. If however, the degradant is shown to be present in the

98D-1168

C4

RLD, therefore, known and "qualified" no added benefit is gained by the generic organization in identifying the degradation product. Therefore we would like to suggest that identification of the compound if "qualified" in the innovator is not necessary.

In addition, if identification is required, we would like to suggest that the requirement for "x-ray crystal analysis" for characterization of degradation products should be removed or at least limited to those cases where chirality of a degradation product may be significant to the analysis of such degradation products. Single crystal x-ray analysis is a very difficult and expensive procedure to perform on a routine basis.

V. REPORTING IMPURITY CONTENTS IN BATCHES

Line 122-124: The reporting level threshold of either 0.05% or 0.10% as a percentage of the drug substance seems relatively high. Most analytical methods today have LOQs which typically allow for much lower levels of quantitation. If the LOQ of the analytical method is lower than the reporting threshold for individual impurities, does this imply that impurities found at levels below the reporting threshold need not be included in the calculation of total degradation products? This should be clarified.

Line 126-128: This line should be modified to read: "In addition, where an analytical procedure reveals the presence of impurities in addition to the degradation products, the origin of these impurities (e.g..,impurities arising from the synthesis of the drug substance) should be discussed." In the original sentence it sounds like what is required is a discussion of the origin of impurities in the synthesis rather than a discussion of the origin of the impurities in the drug product.

Line 131: This line states that the chromatograms should show the location of the observed degradation products and impurities of the drug substance. Does "observed" apply to degradation products and impurities too or just degradation products? It could be misinterpreted the way it is stated currently.

VI. QUALIFYING IMPURITIES

Line 217-219: This section discusses the necessity of obtaining innovator product with an expiration date that precedes the date of manufacture of the innovator product. However, in most cases, the data of manufacture for an innovator product is not readily available. Quite frequently too, only one lot of innovator is available on the market thus eliminating the possibility of selecting

another. Furthermore, the levels of degradation products found in a fresh batch of the RLD are not suitable for setting shelf-life limits of a generic product as these levels may increase over time. We would like to suggest that a lot of RLD close to its expiration date be used to set limits for generic products.

As a final comment, we would like to point out that there are some cases where the innovator product is unavailable or had been discontinued during the development of the product. In those cases, we would like to suggest that there be an alternate mechanism developed perhaps through additional information available from OGD or the use of another market leader that would allow for the qualification of impurities.

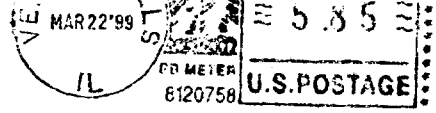
Thank you for our opportunity to comment on this guideline.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director,
Regulatory Affairs

-1811 MAIL



www.usps.gov

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive
Room I-23
Rockville, MD 20857